PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
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Patricia Zilliox
Stella M. Robertson

Serial No.: 10/606,501 (Conf. #6284)

Filed: June 26, 2003

For: USE OF ANECORTAVE ACETATE FOR THE PROTECTION OF VISUAL ACUITY IN PATIENTS WITH AGE RELATED MACULAR DEGENERATION

Group Art Unit: 1618

Examiner: Fay, Z

Atty. Dkt. No.: 2422 US

CERTIFICATE OF MAILING
37 C.F.R 1.8

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APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
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Sir:

This paper is submitted in response to the Final Office Action dated July 14, 2005, for which the three-month date for response was October 14, 2005. A Response to the Final Office Action was timely filed on November 14, 2005. An Advisory Action maintaining the rejections was mailed on January 13, 2006. A Notice of Appeal was timely filed on January 13, 2006. The due date for this Appeal Brief was March 13, 2006.

A request for a three-month extension of time to file this Appeal Brief is included herewith along with the required fee. This three-month extension will bring the due date to June 13, 2006, which is within the six-month statutory period for filing of an Appeal Brief.

Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Alcon, Inc. Deposit Account No. 501051.

I. REAL PARTY IN INTEREST

The real party in interest in this case is Alcon, Inc. The recordation of assignment document is attached hereto as Exhibit B.

II. RELATED APPEALS AND INTERFERENCES

Applicants know of no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-13 were originally filed with the case on June 26, 2003. Claims 1, 5, 9 and 13 were amended and claims 14-18 were added in a Preliminary Amendment filed on October 16, 2003. All pending claims were rejected in an Office Action mailed on September 27, 2004. Claims 1, 4, 5, 8, 9, 11, 14, and 16 were amended and claims 3, 7, 11, and 15 were canceled in a Response to Office Action filed on January 27, 2005.

All pending claims were rejected in a Final Office Action, mailed on July 14, 2005. Claim 1 was amended to correct a typographical error in the claim in a Response to Final Office Action, filed on November 14, 2005. No claims were added or cancelled in response to the Final Office Action.

Therefore, claims 1, 2, 4-6, 8-10, 12-14 and 16-18 are the subject of this appeal. The Appealed claims are set forth in the Claims Appendix.

IV. STATUS OF AMENDMENTS

Claim 1 was amended in the Response to Final Office Action to correct a typographical error in the claim. An Advisory Action mailed on January 13, 2006, indicated that the amendments to the claims made after the final rejection would be entered upon appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to preparations and methods for inhibiting the loss of visual acuity associated with AMD, maintaining visual acuity in persons suffering from AMD, inhibiting lesion growth associated with AMD, and inhibiting blood vessel growth associated with AMD. The methods of the invention include administering to a patient from 3 mg to 30 mg of the compound anecortave acetate or its corresponding alcohol. Preferably, the compound is administered to the patient by posterior juxtascleral injection, juxtascleral implant, intravitreal injection or by implant. (Spec. page 2, lines 3-8; page 8, lines 35-37).

The most preferred amount of anecortave acetate or its corresponding alcohol for use in the methods of the invention is 15 mg. (Spec. page 7, lines 8-11). Where the method of the invention is the inhibition of lesion growth associated with AMD, the preferred lesion types for treatment are predominantly classic subfoveal lesions and minimally classic lesions. (Spec. page 6, lines 4-6. The preferred method of administration for all methods of treatment of the invention is by juxtascleral depot (i.e., posterior juxtascleral administration). (Spec. page 5, lines 29-33).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. **Are claims 1, 2, 4-6, 8-10, 12-14 and 16-18 obvious under 35 U.S.C. §103(a) over Penn and Yaacobi?**

VII. ARGUMENT

A. The Claims are Patentable Over Penn and Yaacobi

The Advisory Action states that the rejection of all pending claims under § 103(a) as being unpatentable over Penn *et al.* and Yaacobi is maintained for "the reasons of record." The Final Action asserts that Penn teaches the use of anecortave acetate in a pharmaceutical formulation for the inhibition of angiogenesis of ocular conditions such as macular degeneration. The Final Action acknowledges that Penn lacks a teaching of the prevention of loss of vision associated with AMD, maintaining visual acuity associated with AMD, the inhibition of lesion growth and the inhibition of blood vessel growth associated with AMD (*i.e.*, the uses claimed in the pending claims). Nevertheless, the Action states that it would have been obvious to use the claimed compound for the claimed uses in light of Penn's teaching of the treatment of macular degeneration. Yaacobi is said to teach the use of a device, which can be implanted into the eye for drug delivery purposes and to mention the use of anecortave acetate in the device. With respect to Applicants' previous arguments, the Action states that the determination of optimum proportions or amounts and route of administration is considered to be within the skill of the artisan. Applicants respectfully traverse.

The Final Action asserts that maintaining visual acuity associated with macular degeneration, inhibiting blood vessel growth associated with macular degeneration and

inhibiting lesion growth associated with macular degeneration would be inherent properties of a composition known for treating macular degeneration. Applicants submit a publication by The Anecortave Acetate Clinical Study Group, published in RETINA, ("the RETINA article;" attached as Exhibit A), which provides evidence to establish the unexpected or unobvious nature of the claimed invention. The RETINA article reports an interim analysis of the data from the first six months of a study designed to compare the clinical efficacy of anecortave acetate versus placebo treatment for preservation (maintenance) of vision and inhibition of CNV lesion growth. These parameters had not been previously studied.

The results indicate that anecortave acetate 15 mg was statistically superior to placebo treatment at month 6 with respect to mean change in logMAR visual acuity, and that treatment with both anecortave acetate 30 mg and 3 mg was favored over placebo treatment (See Fig. 1, page 18). Furthermore, with respect to the preservation of vision in the large subgroup of patients with a predominantly classic CNV lesion, anecortave acetate 15 mg was significantly better than placebo (See Fig. 3, page 19). This superior efficacy for anecortave acetate 15 mg is further supported by data comparing clinically significant vision loss and severe vision loss (See Table 3 and Table 4, respectively, page 17 and page 19). Additionally, anecortave acetate 15 mg was shown to be statistically superior to placebo treatment for inhibition of total lesion surface area, total CNV surface area, and total classic CNV surface area at month 6 (See Fig. 5, page 21). A trend favoring the anecortave acetate 30 mg and 3 mg treatment regimens over placebo treatment for the inhibition of lesion growth was also observed.

The Final Action asserts that "animal models are routinely used as preliminary study models for human use," reasoning that the determination of optimum proportions or amounts

and route of administration is within the skill of the artisan. Applicants submit that, while animal models are routinely use as preliminary study models, their use typically provides evidence of utility or effectiveness of a compound for a particular disease state represented in the animal model. Once a compound's potential effectiveness is shown in animal models, the task of determining the optimal dosage type, amount and frequency is undertaken. It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination or make the resultant modification. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

Moreover, the Board of Patent Appeals and Interferences has held that the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish obviousness. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (BPAI 1993). Section 2143.01 of the MPEP explains the *Levengood* holding as follows:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.

MPEP § 2143.01, page 2100-91 (emphasis in original).

Applicants submit that the Final Action merely states that the modification to the cited art would have been within the ordinary skill of the art without providing the requisite evidence of motivation for the modification. Thus, it is believed that, in light of the unexpected findings of the superiority of the 15 mg dosage and the trend for preference for the 3 mg and 30 mg doses over placebo, and the absence of evidence of motivation for modification of the cited art, the present invention is not obvious over Penn and Yaacobi.

For the foregoing reasons, Applicants respectfully request that the obviousness rejection based on Penn and Yaacobi be withdrawn.

VIII. CLAIMS APPENDIX

Claim 1 (previously presented) A method for inhibiting the loss of visual acuity associated with AMD, which comprises, administering to a patient from 3 mg – 30 mg of the compound anecortave acetate or its corresponding alcohol, wherein said administering is by a method selected from the group consisting of posterior juxtascleral injection, juxtascleral implant, intravitreal injection, or implant.

Claim 2 (original) The method of claim 1, wherein the compound is administered as a juxtascleral depot.

Claim 3 (canceled)

Claim 4 (previously presented) The method of claim 2, wherein the depot comprises 15 mg of compound.

Claim 5 (previously presented) A method for maintaining visual acuity in a person suffering from AMD, which comprises administering to a patient from 3 mg – 30 mg of the compound anecortave acetate or its corresponding alcohol, wherein said administering is by a method selected from the group consisting of posterior juxtascleral injection, juxtascleral implant, intravitreal injection, or implant.

Claim 6 (original) The method of claim 5, wherein the compound is administered as a juxtascleral depot.

Claim 7 (canceled)

Claim 8 (previously presented) The method of claim 6, wherein the depot comprises 15 mg of compound.

Claim 9 (previously presented) A method for the inhibition of lesion growth associated with AMD, which comprises administering to a patient from 3 mg – 30 mg of the compound anecortave acetate or its corresponding alcohol, wherein said administering is by a method selected from the group consisting of posterior juxtascleral injection, juxtascleral implant, intravitreal injection, or implant.

Claim 10 (original) The method of claim 9, wherein the compound is administered as a juxtascleral depot.

Claim 11 (canceled)

Claim 12 (previously presented) The method of claim 10, wherein the depot comprises 15 mg of compound.

Claim 13 (previously presented) The method of any one of claims 1, 5, or 9, wherein the compound is administered in a juxtascleral implant.

Claim 14 (previously presented) A method for inhibiting blood vessel growth associated with AMD, said method comprising administering to a patient from 3 mg – 30 mg of the compound anecortave acetate or its accompanying alcohol, wherein the administering is by juxtascleral injection, intravitreal injection, juxtascleral implant, or other implant.

Claim 15 (canceled)

Claim 16 (previously presented) The method of claim 14, wherein the amount of compound administered is 15 mg.

Claim 17 (previously presented) The method of claim 9, wherein the lesion is a predominantly classic subfoveal lesion.

Claim 18 (previously presented) The method of claim 9, wherein the lesion is a minimally classic lesion.

IX. EVIDENCE APPENDIX

Evidence of assignment of the invention to Alcon, Inc. is attached behind this page.

X. RELATED PROCEEDINGS APPENDIX

None

This is submitted to be a complete Brief on Appeal.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: 13 June 06

EXHIBIT A

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Vol. 23 No. 1 February 2003

ANECORTAVE ACETATE AS MONOTHERAPY FOR THE TREATMENT OF SUBFOVEAL LESIONS IN PATIENTS WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION (AMD)

Interim (Month 6) Analysis of Clinical Safety and Efficacy

THE ANECORTAVE ACETATE CLINICAL STUDY GROUP*

Purpose: To evaluate clinical safety and efficacy of the anglostatic agent anecortave acetate for treatment of subfoveal choroidal neovascularization secondary to AMD.

Methods: 128 patients were randomized to placebo treatment or one of three anecortave acetate doses. Study medication was administered as a posterior juxtascleral injection onto the posterior scleral surface. Best-corrected logMAR vision was obtained at baseline and follow-up visits. Fluorescein angiograms were evaluated for eligibility before enrollment and posttreatment.

Results: Six months after a single treatment, visual acuity (mean change from baseline logMAR values) was significantly better ($P = 0.003$) after anecortave acetate 15 mg than placebo. More patients treated with anecortave acetate 15 mg than placebo maintained vision (88% versus 70%, $P = 0.080$), especially those with predominantly classic lesions (92% versus 65%, $P = 0.021$). Anecortave acetate 15 mg inhibited lesion growth significantly better than placebo ($P = 0.001$). Trends favoring the other doses over placebo were observed for vision preservation and lesion inhibition, but statistical significance was not achieved. The Independent Safety Committee overseeing this study identified no clinically relevant treatment-related changes.

Conclusion: Anecortave acetate 15 mg is safe and effective for preserving or improving vision and for inhibiting lesion growth in patients with subfoveal AMD.

RETINA 23:14–23, 2003

Age-related macular degeneration (AMD) is currently the primary cause of severe vision loss in patients over age 50 in developed countries. Although the exudative form is present in only 15% to 20% of the AMD population, exudative AMD accounts for much of the important vision loss.[1] Until recently, the only approved treatment for choroidal neovascularization (CNV) associated with exudative AMD was laser photocoagulation. In 2000, photodynamic therapy with Visudyne® (Novartis AG, Basel, Switzerland) was approved by the US Food and Drug Administration for the treatment of selected subfoveal lesions in this patient population. However, this treatment option

*See the Appendix for a complete listing of the members of the Anecortave Acetate Clinical Study Group.

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has been shown to delay, but not stop, loss of vision in a majority of the patients treated.[2]

Because irreversible retinal damage due to exudative AMD is the direct result of abnormal choroidal blood vessel growth beneath the retina and/or the retinal pigment epithelium (RPE), a number of angiostatic agents are now being evaluated clinically for use in treating this very serious vision disorder. Angiogenesis is a complex of interrelated processes with numerous potential opportunities for therapeutic intervention. In contrast to other experimental therapies for AMD, which were designed to specifically inhibit angiogenesis stimulated by vascular endothelial growth factor (VEGF),[3,4] anecortave acetate inhibits blood vessel growth by inhibiting the proteases necessary for vascular endothelial cell migration.[5,6] Anecortave acetate is unique in that it inhibits angiogenesis subsequent to (and therefore independently of) the actual angiogenic stimulus, and it therefore has the potential to nonspecifically inhibit angiogenesis driven by the wide variety of known ocular angiogenic stimuli.[7] The ability of anecortave acetate to inhibit angiogenesis independently of the initiating stimulus is supported by a large body of laboratory evidence, including multiple animal models of neovascularization.[6,8–10]

Anecortave acetate is being clinically evaluated as monotherapy to treat exudative subfoveal AMD in this ongoing multicenter trial. The results of an interim analysis of the first 6 months of clinical data on safety and efficacy following a single treatment are reported here.

Methods

This ongoing trial was initiated to compare the clinical efficacy of anecortave acetate versus placebo treatment for preservation (maintenance) of vision and inhibition of CNV lesion growth. Patients with a logMAR visual acuity of 0.3 (20/40 Snellen equivalent) to 1.2 (20/320 Snellen equivalent) and primary or recurrent subfoveal CNV secondary to AMD with a lesion up to 30.48 mm^2 (12 disk areas) in size were enrolled. Because all angiographic data for this study are being collected using the same fundus camera and digital camera systems and stored as uncompressed digital images, the actual lesion surface areas can be more closely approximated in mm^2, rather than requiring the disk area "best-fit" estimates previously used for film angiographic data. Inclusion and exclusion criteria for this study are listed in Table 1. At baseline and follow-up visits, best-corrected logMAR visual acuity was obtained on all patients by masked refractionists using guidelines previously established for the Early Treatment Diabetic Retinopathy Study. Patient lesion eligibility for this study was determined from standardized fluorescein angiograms at the Digital Angiography Reading Center (DARC; New York, NY) by certified Readers (trained retina specialists) before enrollment and treatment. Using the modified definitions established by the Macular Photocoagulation Study Group,[11] eligible lesions extended under the geometric center of the foveal avascular zone. Initially, only patients with total lesion areas of 12.7 mm^2 or less (the arithmetic equivalent of 5 disk areas) were eligible for treatment. This criterion was amended in August 1999 to allow treatment of subfoveal lesions 30.48 mm^2 or less in actual area (the arithmetic equivalent of 12 disk areas) to allow completion of patient enrollment. Eligible subfoveal lesions were also re-

Table 1. Principal Patient Inclusion and Exclusion Criteria

Inclusion Criteria
• Aged ≥50 yr.
• Exudative AMD and primary/recurrent subfoveal CNV ≤ 30.48 mm^2 (arithmetic equivalent of 12 MPS disk areas) in size. Angiographic evidence that CNV occupies at least 50% of the total lesion area. The area of CNV must be composed of at least 50% classic CNV, or the area of the classic CNV must be at least 1.6 mm^2 (arithmetic equivalent of 0.75 disk areas).
• Best-corrected ETDRS visual acuity of 0.3 (20/40 Snellen equivalent) to 1.2 (20/320 Snellen equivalent) in the study eye at the eligibility visit. The fellow eye must have clinical evidence of macular degeneration, with a visual acuity of 1.6 (20/800 Snellen equivalent) or better.
• Willing to give and sign informed consent; able to make the required study visits.
Exclusion Criteria
• Medical history or clinical evidence of preexisting ophthalmic disease in the study eye (other than AMD) that during follow-up would likely compromise the visual acuity of the study eye.
• Clinical evidence of myopic retinopathy, or a refraction of greater than −8 diopter power.
• Intraocular surgery in study eye less than 2 months before enrollment.
• History of previous experimental treatment for AMD in the study eye other than laser photocoagulation.
• Presence of a scleral buckle in the study eye.
• Use of any investigational drug or treatment related or unrelated to AMD within 30 days before enrollment.
• Medical history of a bleeding disorder or need for anticoagulant therapy other than antiplatelet therapy.
• Clinical evidence of scleral thinning.

AMD, age-related macular degeneration; CNV, choroidal neovascularization; ETDRS, Early Treatment of Diabetic Retinopathy Study.

quired at baseline to have the classic CNV component occupy at least 50% of the measurable area of total CNV or to have a classic component at least 1.6 mm^2 in size (the arithmetic equivalent of 0.75 disk areas). As a result of this amendment, 20% of the patients had minimally classic lesions at baseline. DARC readers also evaluated changes from baseline in the fluorescein angiographic characteristics of the lesions in masked fashion. Each data point represents the average of at least two independent evaluations by DARC readers.

The 128 patients in this double-masked, dose-response study were enrolled and treated between April 1999 and May 2001 by 18 participating sites in the United States and European Union. Before treatment, patients were enrolled and equally randomized to anecortave acetate sterile suspension for injection 30 mg (n = 33), 15 mg (n = 33), or 3 mg (n = 32) or to placebo (vehicle, n = 30). Masking of the clinical sites as to treatment group is being maintained in two ways. Study medication is masked by placing the treatment kits, which include study medication and supplies for the posterior juxtascleral administration, in sealed opaque boxes identified by patient number only. The boxes were numbered sequentially at each clinical site, and patients were assigned the next available sequential number on enrollment. The randomization was built into the sequential numbering of the treatment kits and blocked within each site to maintain equal distribution across treatment assignments. Masking of treatment is also being maintained at each site by having an unmasked injecting investigator perform the treatments and the day 1–2 visit and a masked examining investigator perform the other evaluations. On enrollment of each patient, anecortave acetate or placebo was administered behind the eye as a 0.5 mL posterior juxtascleral injection onto the outer surface of the sclera near the macula using a specially designed cannula.

Clinical efficacy data are being obtained from evaluations of best-corrected logMAR visual acuity (using a per-protocol refraction procedure) and from standardized fluorescein angiograms. Clinical safety data, obtained from general physical examinations, laboratory evaluations of blood and urine, and complete detailed ophthalmic examinations, including indocyanine green angiography, continue to be evaluated periodically by the Independent Safety Committee overseeing this study. Clinical data from evaluations for safety and efficacy performed at day 1–2, week 2, week 6, month 3, and month 6 following patient randomization and treatment are reported here.

The primary efficacy outcome for this ongoing study is the mean change from baseline in best-corrected logMAR visual acuity. Secondary efficacy outcomes are as follows: the percentage of patients with preservation or maintenance of vision (defined as loss of less than three logMAR lines [less than 15 logMAR letters] of visual acuity); the percentage of patients with clinically significant worsening of vision (defined as a loss of at least three logMAR lines [at least 15 logMAR letters] of visual acuity); the percentage of patients with severe vision loss (defined as a loss of at least six logMAR lines [at least 30 logMAR letters] of visual acuity); and changes in CNV lesion characteristics (defined as total lesion area, total CNV, and total classic CNV).

With 30 evaluable patients per group, there was more than 80% power to detect a difference between treatment means of 0.21 logMAR lines assuming a standard deviation (SD) of 0.285 and a 5% chance of a type I error. The SD was calculated using data from a previous study.[11] All efficacy analyses were based on the intent-to-treat principle. All patients received the medication to which they were assigned, and were analyzed accordingly. Fifteen of the 128 patients in this study exited before their month 6 visit. Of the four patients exiting early from the placebo group, one exited for disease progression, one for vision loss, and two for personal reasons. One patient exited early from the 30 mg group for disease progression. Of the eight patients exiting early from the 15 mg group, one exited per investigator decision, two exited for unrelated adverse events (one myocardial infarction, one for stomach pain), two were lost to follow-up, and three left for personal reasons. Two patients exited early from the 3 mg group: one for disease progression and one was lost to follow-up. Last-observation-carried-forward was used to impute missing values. Baseline comparisons were tested using analysis of variance (for continuous outcomes) and either Pearson chi-square or Fisher exact tests (for binary outcomes). Changes from baseline in visual acuity and lesion parameters were tested in a repeated-measures analysis of variance model. Comparisons of binary outcomes at month 6 were evaluated using either Pearson chi-square or Fisher's exact tests. Ocular outcomes were based on changes in the treated eye. All analyses were conducted using SAS® (SAS Institute Inc., Release 8.2, Cary, NC).

In this ongoing study, retreatment with study medication is being performed by the unmasked injecting investigator if the masked examining investigator judges that the patient may benefit. A 6-month retreatment interval was established for this ongoing study based on laboratory data demonstrating that anecortave acetate administered as a slow-release depot adjacent to the posterior scleral surface provided thera-

Table 2. Baseline Patient Characteristics

Characteristics	Anecortave Acetate 30 mg (n = 33)	Anecortave Acetate 15 mg (n = 33)	Anecortave Acetate 3 mg (n = 32)	Placebo (n = 30)	*P* Value
Age, yr, n (%)					
<65	4 (12.1)	5 (15.2)	1 (3.1)	0 (0.0)	0.335
65–74	7 (21.2)	7 (21.2)	9 (28.1)	8 (26.7)	
75–84	19 (57.6)	17 (51.5)	15 (46.9)	19 (63.3)	
85–93	3 (9.1)	4 (12.1)	7 (21.9)	3 (10.0)	
Female sex, n (%)	18 (54.5)	18 (54.5)	15 (46.9)	18 (60.0)	0.778
Caucasian, n (%)	33 (100.0)	33 (100.0)	32 (100.0)	30 (100.0)	—
Total lesion classic component,* n (%)					
<50%	7 (21.2)	8 (24.2)	7 (21.9)	4 (13.3)	0.733
≥50%	26 (78.8)	25 (75.8)	25 (78.1)	26 (86.7)	
Age, yr, mean (SD)	75.7 (7.5)	75.8 (8.3)	78.1 (7.5)	78.3 (5.8)	0.319
logMAR VA, mean (SD)	0.72 (0.26)	0.73 (0.26)	0.83 (0.24)	0.76 (0.26)	0.286
Total lesion mm^2, mean (SD)	8.6 (6.9)	7.4 (6.6)	9.0 (7.5)	6.9 (5.7)	0.580
CNV mm^2, mean (SD)	7.4 (6.0)	6.4 (5.5)	7.9 (7.0)	6.0 (5.2)	0.572
Classic mm^2, mean (SD)	5.7 (5.3)	5.0 (5.0)	5.3 (4.7)	4.2 (4.2)	0.685

* Determined from the ratio of the size of the classic component to the size of the total lesion.
VA, visual acuity; SD, standard deviation; CNV, choroidal neovascularization.

peutic drug levels in the adjacent choroid and retina for up to 6 months (data not shown). Sixty-two of the 128 patients enrolled in this study have received at least three posterior juxtascleral administrations of anecortave acetate or placebo at 6-month intervals, while 26 patients have received at least five such treatments. As of November 2002, 47 patients continue to be treated with masked study medication at 6-month intervals in this ongoing study. However, the efficacy results presented here are based on a single (initial) administration of study medication.

Results

There were no statistically significant differences in baseline values among treatment groups with respect to age, sex, race, logMAR visual acuity, or lesion characteristics (Table 2). Of the 128 patients in this study, 80% (102 of 128) entered the study with predominantly classic lesions, while 20% (26 of 128) entered with minimally classic lesions. A predominantly classic lesion is defined as one in which classic CNV occupies at least 50% of the area of the total lesion (defined for this study as angiographic evidence of neovascularization, associated contiguous areas of serous elevation of the RPE, elevated blocked fluorescence, blood, and/or late staining). The baseline patient characteristics in this study were generally similar to those reported for the Visudyne® TAP trial,[2] except that a greater percentage (80% versus 40%) of the patients in the study reported here had predominantly classic lesions at baseline.

An interim analysis of all 128 patients was performed to evaluate mean change at month 6 from baseline values in logMAR visual acuity (Table 3 and Figure 1). Anecortave acetate 15 mg was statistically superior to placebo treatment ($P = 0.003$) at month 6. Trends also favor treatment with both anecortave acetate 30 mg and 3 mg over placebo treatment, al-

Table 3. Summary Statistics for LogMAR Visual Acuity Change From Baseline

Visit	Anecortave Acetate 30 mg (n = 33)	Anecortave Acetate 15 mg (n = 33)	Anecortave Acetate 3 mg (n = 32)	Placebo (n = 30)
Baseline	0.72 (0.26)	0.73 (0.26)	0.83 (0.24)	0.76 (0.26)
Week 2	0.04 (0.15)	0.01 (0.14)	0.04 (0.17)	0.04 (0.14)
Week 6	0.10 (0.21)	0.00 (0.14)	0.04 (0.18)	0.08 (0.16)
Month 3	0.15 (0.28)	0.04 (0.22)	0.11 (0.22)	0.10 (0.25)
Month 6	0.18 (0.27)	0.08 (0.24)	0.19 (0.27)	0.25 (0.37)

Baseline results are mean logMAR acuity values.

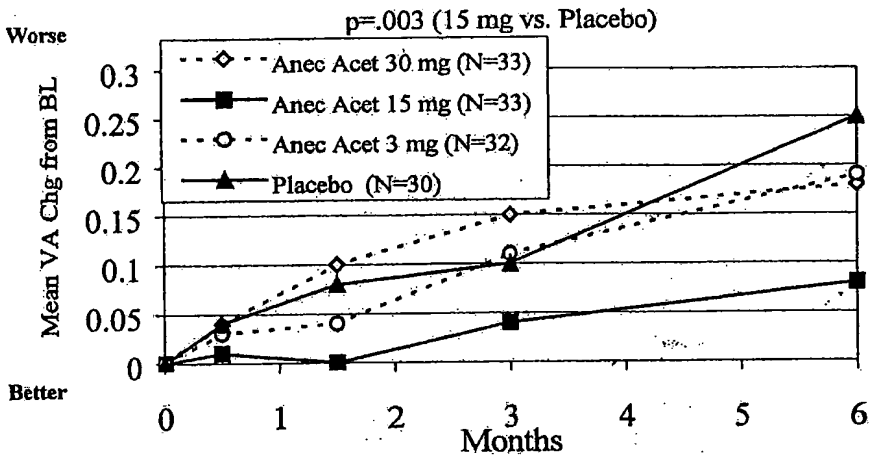

Fig. 1. When mean change from baseline logMAR visual acuity at month 6 is compared among treatment groups, there is a statistically significant difference (P = 0.003) between treatment with anecortave acetate (Anec Acet) 15 mg and placebo treatment. After a single treatment of anecortave acetate 15 mg, mean logMAR vision changes at month 6 by less than one line (four logMAR letters) to a +0.08 logMAR score. In contrast, after a single placebo treatment the mean logMAR vision had worsened by more than two lines (12 logMAR letters) to a +0.24 logMAR score over the same period.

though statistical significance was not achieved. Of the four groups, anecortave acetate 15 mg exhibits the greatest efficacy for stabilizing vision.

As a secondary visual outcome, the percentage of patients with preservation of vision at month 6 was analyzed. Preservation (maintenance) of vision, defined as a decrease of less than three logMAR lines of visual acuity from baseline values, is accepted as a clinically relevant measure of efficacy and has been used as a primary outcome variable in a previous report evaluating therapy for subfoveal AMD.[2] The 6-month results of this analysis are presented in Figure 2. There was greater preservation of vision for patients treated with anecortave acetate 15 mg than for placebo, although the results did not achieve statistical significance at the P = 0.05 level. Whereas 88% of patients treated with anecortave acetate 15 mg had preserved vision at month 6, only 70% of placebo-treated patients showed a similar positive visual outcome (P = 0.080). However, as shown in Figure 3, analysis of these data in the large subgroup of patients with a predominantly classic CNV lesion revealed a significant benefit favoring anecortave acetate 15 mg, with 92% of patients treated with this regimen preserving vision at month 6 versus 65% of patients in the placebo group (P = 0.021). The efficacy of anecortave acetate 15 mg for preserving vision is further supported by data comparing clinically significant vision loss (Table 3) and severe vision loss (Table 4) among treatment groups. In both analyses, there is a trend favoring treatment with anecortave acetate 15 mg compared to placebo treatment for prevention of vi-

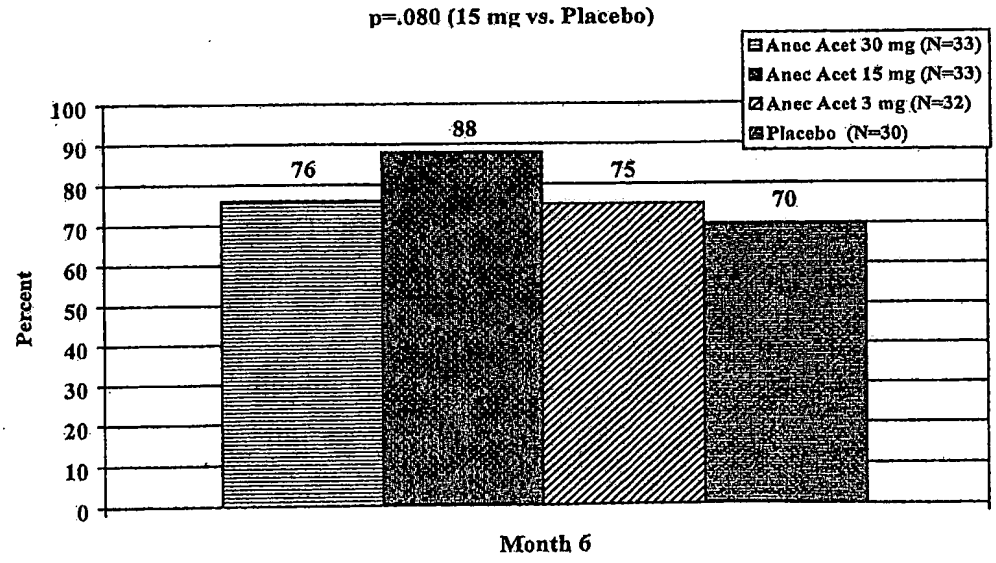

Fig. 2. Comparison of all 128 patients in the four treatment groups as to preservation of vision at month 6, defined as a decrease of less than three logMAR lines or 15 logMAR letters from baseline values. Although statistical significance is not achieved in this analysis, there is a clear trend favoring the anecortave acetate (Anec Acet) 15 mg treatment group over placebo treatment.

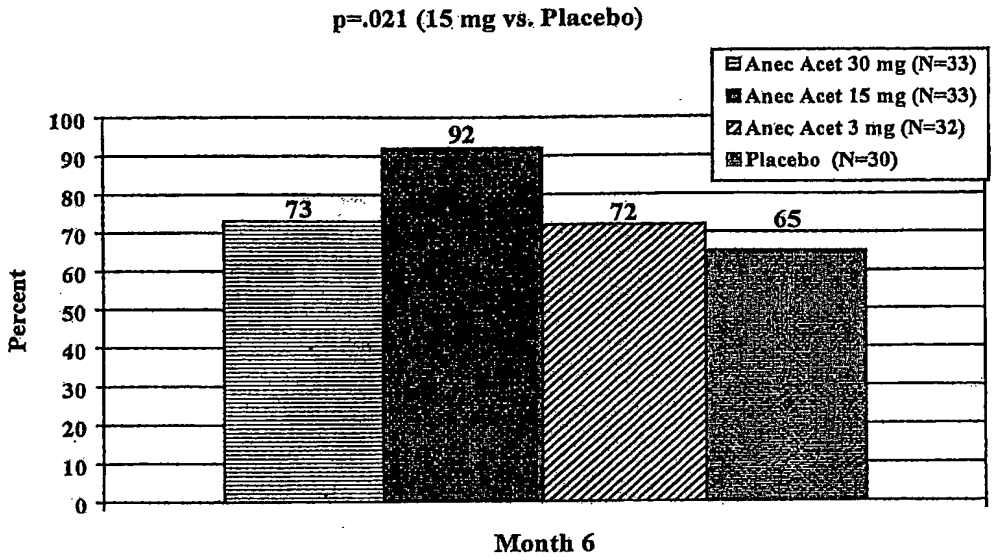

Fig. 3. Subgroup analysis comparing the effect of the four treatment groups for preservation of vision at month 6 in patients with predominantly classic lesions at baseline. There is statistical significance ($P = 0.021$) when the anecortave acetate (Anec Acet) 15 mg treatment group is compared with placebo treatment for this large subgroup of patients.

sion loss, although this did not reach statistical significance.

Figure 4 shows the results of an analysis of the percentage of patients with an improvement of at least two logMAR lines in visual acuity from baseline values. Eighteen percent of patients treated with anecortave acetate 15 mg improved by at least two logMAR lines, compared with 3% of patients in the 30 mg group, 6% in the 3 mg group, and 0% in the placebo group. The difference between anecortave acetate 15 mg and placebo was statistically significant ($P = 0.025$).

Because of laboratory data demonstrating anecortave acetate's angiostatic efficacy, CNV lesion changes from baseline values in surface areas were analyzed. Total lesion areas, total CNV areas, and total classic CNV areas were measured and compared among treatment groups. Although the average lesion size was similar among the treatment groups at baseline, the variability within treatment groups reduced

Table 4. Clinically Significant LogMAR Vision Changes at Month 6

Treatment	LogMAR Change					
	≥2 Lines Improved	1 Line Improved	No Change	1 Line Worsened	2 Lines Worsened	≥3 Lines Worsened
Anecortave acetate, mg						
30	1 (3.0)	4 (12.1)	10 (30.3)	5 (15.2)	5 (15.2)	8 (24.2)
15	6 (18.2)	1 (3.0)	8 (24.2)	4 (12.1)	10 (30.3)	4 (12.1)
3	2 (6.3)	0 (0)	12 (37.5)	4 (12.5)	6 (18.8)	8 (25.0)
Placebo	0 (0)	2 (6.7)	11 (36.7)	4 (13.3)	4 (13.3)	9 (30.0)

Values are expressed as n (%).
$P = 0.120$ (15 mg vs placebo) for <3 line worsening vs ≥3 line worsening. Fisher exact test.

Table 5. Severe Vision Loss (≥6 LogMAR lines) at Month 6

Treatment	Total n	<6 Line Loss, n (%)	≥6 Line Loss, n (%)
Anecortave acetate			
30	33	29 (87.9)	4 (12.1)
15	33	32 (97.0)	1 (3.0)
3	32	28 (87.5)	4 (12.5)
Placebo	30	25 (83.3)	5 (16.7)
Total	128	114 (89.1)	14 (10.9)

$P = 0.094$ (15 mg vs placebo), Fisher exact test.

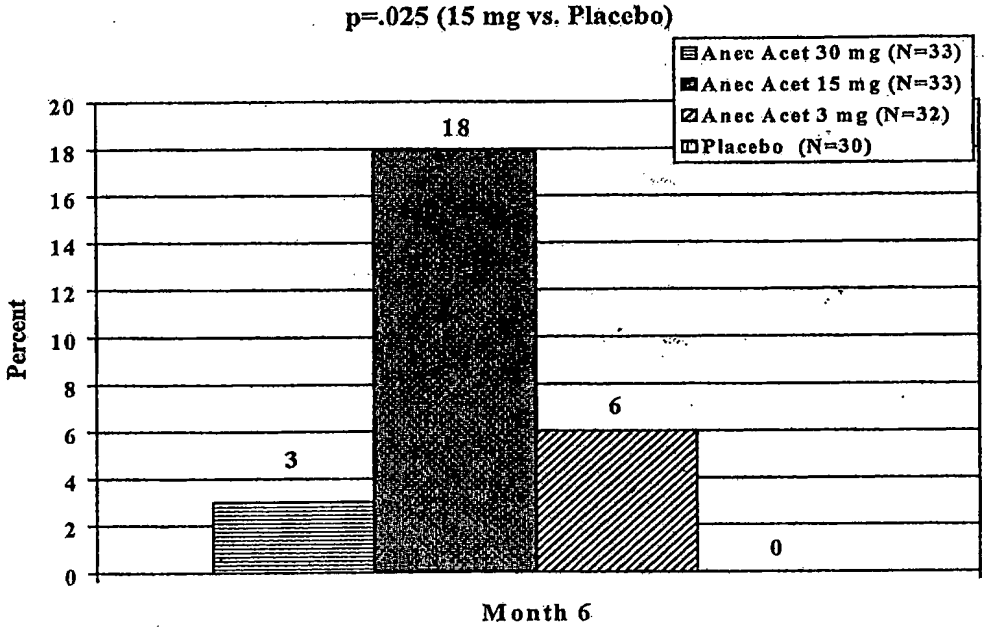

Fig. 4. The percentage of patients with improved vision, defined as an increase of at least two logMAR lines or 10 logMAR letters of visual acuity at month 6 compared with baseline values. This overall analysis of all 128 patients enrolled in the study reveals a statistically significant positive effect of anecortave acetate (Anec Acet) 15 mg for improvement of vision at month 6 ($P = 0.025$) compared with placebo.

the sensitivity to demonstrate group differences when the groups were analyzed for mean change from baseline values. Changes in these lesion characteristics were therefore analyzed as percent change from baseline values, which proved to be a more sensitive measure for evaluating a population of lesions that ranged from 0.28 mm^2 to 33.25 mm^2 in total lesion areas at baseline. As shown in Figure 5, treatment with anecortave acetate 15 mg is statistically superior to placebo treatment for inhibition of total lesion surface area ($P < 0.001$), total CNV surface area ($P < 0.001$), and total classic CNV surface area ($P = 0.001$) at month 6. In addition, there is a trend favoring the anecortave acetate 30 mg and 3 mg treatment regimens over placebo treatment for the inhibition of lesion growth.

After completion of the month 6 visit by all patients, the accumulated safety data were evaluated by the Independent Safety Committee overseeing this study. Based on this evaluation, no clinically relevant medication-related or administration-related safety concerns were identified. The most common ocular changes reported were changes in lens opacity using the Lens Opacity Classification System (LOCS) II, and included reports of nuclear color, nuclear opalescence, cortical, and posterior subcapsular changes. Cataracts are a common intercurrent disorder in this patient population, and the changes seen were documented in all treatment groups (including the placebo group) and in contralateral (untreated) eyes. The cataractous changes reported were described as mild and typically unrelated to treatment. The second most common ocular change, a decrease in vision (defined as a decrease of greater than or equal to four logMAR lines from the previous visit), is also a common problem in this patient population. These vision decreases occurred in all treatment groups (including the placebo group) and in the contralateral eye. Other ocular changes (occurring with a frequency greater than 5%) were ptosis, ocular pain, subconjunctival hemorrhage, ocular pruritis, ocular burning/stinging, pupil disorders, foreign body sensation, ocular hyperemia, and abnormal vision. These changes were reported in all four treatment groups, in both treated eyes and contralateral eyes, and were characterized as primarily mild, generally not attributed to treatment, and transient in nature. The single report of an intraocular pressure increase ($\geq$10 mmHg) from baseline occurred in a patient treated with anecortave acetate 30 mg and was attributed to intercurrent illness. Of the ocular changes reported, those most frequently attributed to study treatment were ptosis, ocular pain, subconjunctival hemorrhage, ocular pruritis, and ocular burning/stinging. These treatment-related events were mostly mild, transient, and seen within all four treatment groups.

The most common nonocular changes from baseline reported for this study were hypertension, peripheral edema, depression, and arthritis, none of which was attributed to treatment. No treatment-related changes in blood chemistry, hematology, or urinalysis were reported.

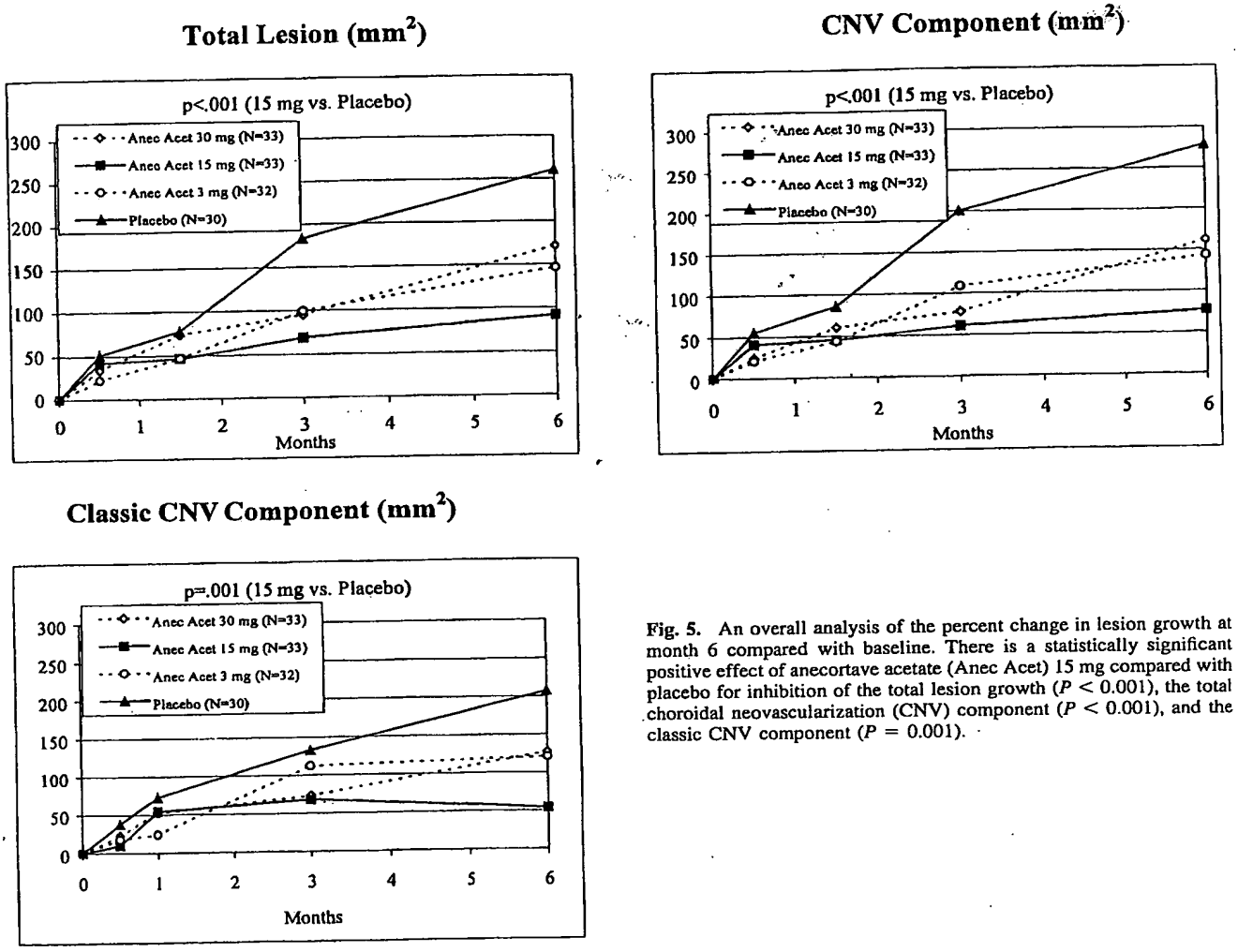

Fig. 5. An overall analysis of the percent change in lesion growth at month 6 compared with baseline. There is a statistically significant positive effect of anecortave acetate (Anec Acet) 15 mg compared with placebo for inhibition of the total lesion growth ($P < 0.001$), the total choroidal neovascularization (CNV) component ($P < 0.001$), and the classic CNV component ($P = 0.001$).

Discussion

The efficacy data reported here are the result of an interim analysis of the first 6 months of clinical data from the ongoing study evaluating anecortave acetate as monotherapy for treatment of exudative AMD. The safety summary includes all data available at the time of the month 6 efficacy analysis. This analysis demonstrates that a single posterior juxtascleral administration of anecortave acetate 15 mg is a safe and effective treatment for preserving or improving vision as well as preventing severe vision loss. These data also show that anecortave acetate inhibits lesion growth in patients with subfoveal CNV secondary to AMD. Although there is a trend favoring a single administration of each of the three concentrations of anecortave acetate over placebo treatment, only anecortave acetate 15 mg is statistically superior to placebo for both functional and anatomical measures of clinical efficacy.

Anecortave acetate is a synthetic corticosteroid derivative specifically modified to eliminate its corticosteroid activity in vivo. Laboratory data show that anecortave acetate exhibits no measurable corticosteroid activity[8,9] and there is no clinical evidence of ocular corticosteroid side effects (such as elevated intraocular pressure or accelerated cataract progression) in the study reported here. After an evaluation of safety data from patients with at least 6 months of anecortave acetate exposure, the Independent Safety Committee identified no clinically relevant drug-related or procedure-related safety issues. It is important to note that the safety data reported reflect an evaluation of all available data on all patients at the time of the month 6 visit by the last study patient. These data include information on patients enrolled in the study for up to 2 years, with multiple retreatments. Although these data are too limited to make solid predictions as

to clinical safety following wider use over longer periods, they are nonetheless very promising.

Anecortave acetate is a unique angiostatic agent that inhibits both urokinaselike plasminogen activator and matrix metalloproteinase-3, two enzymes necessary for vascular endothelial cell migration during blood vessel growth.[5,6] Laboratory data in models of corneal, retinal, and choroidal neovascularization support the efficacy of this agent for the inhibition of vessel growth.[5,6,8–10]

The interim analysis of clinical data reported here demonstrates angiostatic efficacy at month 6 after a single posterior juxtascleral administration, based on the masked evaluation of standardized fluorescein angiograms by DARC, the central reading center used for this study. This analysis shows that anecortave acetate 15 mg is statistically superior to placebo at month 6 for inhibition of lesion growth. There was inhibition not only of total lesion growth but also of the CNV component and the classic CNV lesion component.

As might be expected of a treatment that inhibited lesion growth, analysis of the month 6 data demonstrate a trend favoring anecortave acetate 15 mg over placebo treatment for preservation of vision in the overall analysis, and statistical superiority for preserving vision in the large subgroup of patients with predominantly classic lesions. Anecortave acetate 15 mg is also statistically superior to placebo for vision improvement, defined as an improvement of two or more lines of logMAR visual acuity. This superiority of anecortave acetate 15 mg is supported by trends favoring anecortave acetate 15 mg over placebo for prevention of both clinically significant and severe vision loss, although these trends were not statistically significant.

The superiority of the anecortave acetate 15 mg dose compared with placebo for stabilizing vision is demonstrated by the analysis of mean change at month 6 from baseline logMAR vision. Although the mean baseline logMAR vision was very similar for the anecortave acetate 15 mg and placebo groups (0.73 versus 0.76, respectively, or 20/100 Snellen equivalent), the vision outcome at month 6 was distinctly different for these two treatment groups. After treatment with a single administration of anecortave acetate 15 mg, the mean vision changed by only four logMAR letters at month 6, resulting in an average final logMAR value of 0.81 (20/125 Snellen equivalent). However, the placebo group over the same period worsened by more than 12 logMAR letters, resulting in an average final value of 1.01 (20/200 Snellen equivalent). This two-line difference between groups in logMAR visual acuity is likely to have implications for the daily activities of a patient with subfoveal AMD.

The statistical superiority of anecortave acetate 15 mg over placebo was demonstrated at the 0.0032 level of significance for the primary efficacy variable. Owing to multiple comparisons involving each anecortave acetate concentration versus placebo, a Bonferroni correction was applied, meaning the observed *P* value for each comparison of the primary efficacy variable should be assessed at the 0.017 significance level. We note that even with this correction, the primary result remains statistically significant. However, it is important to remember that these data represent an interim analysis at month 6.

All three doses of anecortave acetate have been shown to be safe, and following a single administration there is a trend at month 6 favoring the three doses for inhibition of lesion growth, preservation of vision, and prevention of severe vision loss. The clinical data reported here suggest that the 15 mg dose is at or near the top of the biologic dose-response curve for this molecule, and higher concentrations are not likely to be associated with greater efficacy in vivo. The reasons for the differences between the 15 mg and 30 mg results are not well understood, but may be due to differences in the formation and physical structure of the slow-release drug depot on the posterior scleral surface resulting from the different concentrations of drug suspension evaluated in this study. This could, in some way, affect the absorption of the anecortave acetate into the overlying choroid and retina.

It is important to remember that the results reported here are based on an interim analysis after all patients had the opportunity to complete at least 6 months of follow-up. All patients are planned to be followed for up to 12 months for a final analysis of efficacy data, and for up to 24 months for a final analysis of safety data. A publication is planned for final data analysis to confirm the 6-month interim findings.

The clinical efficacy of anecortave acetate 15 mg compared with placebo for prevention of both clinically significant vision loss (defined as a loss of 15 or more logMAR letters) and severe vision loss (defined as a loss of 30 or more logMAR letters) at month 6 is at least comparable to similar month 6 data reported for the Visudyne® TAP study.[2] In view of the consistent superiority of a single administration of anecortave acetate 15 mg compared with placebo treatment for preservation of vision and for inhibition of lesion growth, a pivotal study has been initiated to compare anecortave acetate 15 mg with Visudyne® PDT. This study is now enrolling patients, and will include up to 50 clinical sites in North America, Australia, and the European Union.

Appendix

Alcon Anecortave Acetate Clinical Study Group

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Key words: anecortave acetate, age-related macular degeneration (AMD), choroidal neovascularization (CNV), angiogenesis, angiostatic agents.

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